REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1 and 54 are amended, claims 4 and 10-12 are canceled, and claims 58-60 are added; as a result, claims 1-3, 5-9, 13-31, and 44-60 are now pending in this application.

Claims 1, 8-9, 15-19, 23, 25, and 44-55 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. This rejection is respectfully traversed.

The Examiner asserts that the specification teaches the structure of only a single representative species of SEQ ID NO:2, 3 and 4 and the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of hybridizing to SEQ ID NO:2, 3 or 4, and given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

The Examiner also asserts that while it is agreed that with aid, one of skill in the art could identify all the nucleic acid sequence with at least 80% sequence identity to SEQ ID NO:2, 3 or 4, there is no teaching regarding which 20% of the nucleotides can vary from SEQ ID NO:2, 3 or 4 and still result in oligonucleotides that form effective hybrids thereby detecting or determining *vanA* in a sample, there is no disclosed or art-recognized correlation between any structure other than SEQ ID NO:2, 3 or 4, the specification does not place any structure, chemical functional limitations on the polynucleotide probe *per se*, and the recitation of primers hybridizing does not convey a common structure or function.

As the Examiner did not provide an explanation in response to Applicant's query in the Amendment filed on May 5, 2008, it is still unclear to Applicant's Representatives why claims 54-55 are rejected under § 112(1) as lacking written description, given that the specification teaches SEQ ID NO:2, 3 and 4. Clarification on this issue is respectfully requested with the next official communication.

The Examiner is respectfully reminded that Applicant need not teach what is well known to the art. *vanA* sequences, including *vanA*-specific probes and primers, were well known to the

art, as were amplification and hybridization assays to detect those and other sequences (see Petrich et al., Mol. Cell Probes, 13:275 (1999) and U.S. Patent No. 6,274,316; both of record, as well as the Table of Contents for Diagnostic Molecular Microbiology: Principles and Applications, Pershing, ed., American Society of Microbiology, 1993 (of record). Moreover, Applicant's specification clearly identifies the nucleotide sequence corresponding to nucleotides 870 to 896, 851 to 868 and 898 to 917 of *vanA* (see Figure 1 and SEQ ID NOs. 2-4).

The Examiner cannot reasonably contend that the recitation of a primer or probe that forms a hybrid with, and has at least 80% contiguous nucleic acid sequence identity to, a particular nucleic acid structure does not convey a common structure or function. Hybrid formation and percent nucleic acid sequence identity between two nucleic acid molecules *clearly* convey a common structure (see, for example, the Table of Contents for Diagnostic Molecular Microbiology: Principles and Applications, Pershing, ed., American Society of Microbiology, 1993; The Polymerase Chain Reaction, Mullis et al., eds., Birkhauser, 1994 (of record), and Molecular Cloning: A Laboratory Manual, Sambrook et al., eds., Cold Spring Harbor Press, 2001 (of record)).

The Examiner also cannot reasonably contend that the skilled artisan cannot envision the detailed structure of nucleic acid sequences with at least 80% contiguous nucleic acid sequence identity to SEQ ID NO:2, 3 or 4. For instance, SEQ ID NO:2 has 18 nucleotides, SEQ ID NO:3 has 27 nucleotides, and SEQ ID NO:4 has 20 nucleotides. A sequence with 3 nucleotide substitutions relative to SEQ ID NO:2 has 83% identity thereto, a sequence with 6 nucleotide substitutions relative to SEQ ID NO:3 has 81% identity thereto, and a sequence with 4 nucleotide substitutions relative to SEQ ID NO:4 has 80% identity thereto

Moreover specifically, SEQ ID NO:2 corresponds to CCGGTGGCAGCTACGTTT (18 nucleotides). 80% of 18 is 14.4. Therefore, probes within the scope of invention include those with up to 3 nucleotide substitutions in SEQ ID NO:2. The following represents a set of variants of SEQ ID NO:2 with a single substitution (indicated by underlining): CGGGTGGCAGCTACGTTT, CAGGTGGCAGCTACGTTT, and CTGGTGGCAGCTACGTTT. The following represents a set of variants of SEQ ID NO:2 with two substitutions (indicated by underlining): CGGGTGGCAGCTAGGTTT, CAGGTGGCAG CTAAGTTT, and CTGGTGGCAGCTATGTTT, and the following represents a set of variants

of SEQ ID NO:2 with three substitutions (indicated by underlining): CGGGGGGCAG CTAGGTTT, CAGGAGGCAGCTAAGTTT, and CTGGCGGCAGCTATGTTT.

Further, prior to Applicant's filing, one of skill in the art was aware that there were conserved regions in *van*A sequences that allowed for amplification of those sequences from clinical samples (see, e.g., Patel et al. (J. Clin. Invest., 35:703 (1997); Patel et al. (Antimicro. Agents Chemothera., 42:202 (1998); and Woodford et al. (Antimicro. Agents Chemothera., 42:502 (1998); a copy of each is enclosed herewith). In addition, Patel et al. (1998) disclose that 9/10 *van*A sequences from clinical isolates differed from a reference strain by only one base pair and one amino acid, while the other isolate had an identical sequence to that of the reference strain.

Given that the Example in the specification discloses the use of SEQ ID Nos. 2-4 in a method to detect *van*A sequences in a sample, that the specification discloses that sequences with close structural relatedness to SEQ ID Nos. 2-4, e.g., those with at least 80% contiguous nucleic acid sequence identity to the 18 nucleotides corresponding to SEQ ID NO;2, the 27 nucleotides corresponding to SEQ ID NO:3, and the 20 nucleotides corresponding to SEQ ID NO:4, are useful in the claimed methods, and that one of skill in the art was aware of, and so could envision, the structure of various regions in *van*A, one of skill in the art would recognize that Applicant was in possession of the genus of recited primers and probes.

Therefore, the recited primers and probes are adequately described.

Claims 1, 8-9, 15-19, 23, 25, and 44-57 were rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. In particular, the Examiner asserts that there is no teaching of the *vanA* specific oligonucleotide probe that consists of 15 to 40 nucleotides with at least 80% nucleic acid sequence identity to SEQ ID NO:3 or the complement of SEQ ID NO:3 that hybridizes to SEQ ID NO:3, a first oligonucleotide primer that has at least 80% nucleic acid sequence identity to SEQ ID NO:2, wherein the first primer hybridizes to the complement of SEQ ID NO:2, and a second oligonucleotide primer has at least 80% nucleic acid sequence identity to SEQ ID NO:4 and wherein the second primer hybridizes to the complement of SEQ ID NO:4. This rejection is respectfully traversed.

The fundamental inquiry with regard to new matter is whether the material added by amendment was inherently contained in the original application. *Litton Sys., Inc. v. Whirlpool*

Corp., 728 F.2d 1423, 1438, 221 U.S.P.Q. 97, 106 (Fed. Cir. 1984). The issue is not whether a specific new word of a claim was used in the specification as filed but whether the concept expressed by the word was present. *In re Anderson*, 471 F.2d 1237, 176 U.S.P.Q. 331 (C.C.P.A. 1973).

As filed, claim 1 recited that the *vanA*-specific oligonucleotide probe comprises sequences which include sequences substantially corresponding to nucleotides 870 to 896 of the *vanA* gene, the complement thereof, or a portion thereof, sequences substantially corresponding to nucleotides 851 to 868 of the *vanA* gene, the complement thereof, or a portion thereof, or sequences substantially corresponding to nucleotides 898 to 917 of the *vanA* gene, the complement thereof, or a portion thereof.

Claim 32 (as filed) is directed to an oligonucleotide composition comprising a first oligonucleotide comprising sequences substantially corresponding to nucleotides 870 to 896 of the *vanA* gene, the complement thereof, or a portion thereof, an oligonucleotide comprising sequences substantially corresponding to nucleotides 851 to 868 of the *vanA* gene the complement thereof, or a portion thereof, an oligonucleotide comprising sequences substantially corresponding to nucleotides 898 to 917 of the *vanA* gene, the complement thereof, or a portion thereof, or a combination thereof, wherein the oligonucleotide hybridizes under stringent hybridization conditions to *vanA* DNA. Claim 34 (as filed) depends on claim 32, and is directed to at least one oligonucleotide that has the length and sequence of any of SEQ ID NOs:2-4.

Pages 10 and 11 of the specification disclose that:

> An "oligonucleotide" is a polynucleotide having two or more nucleotide subunits covalently joined together.
>
> A "primer" is a single-stranded polyoligonucleotide that combines with a complementary single-stranded target to form a double-stranded hybrid, which primer in the presence of a polymerase and appropriate reagents and conditions, results in nucleic acid synthesis.
>
> A "probe" is a single-stranded polynucleotide that combines with a complementary single-stranded target polynucleotide to form a double-stranded hybrid.

Page 6 of the specification discloses:

> In one embodiment, the oligonucleotides of the invention include sequences substantially corresponding to nucleotides 851 to 868 of the *vanA* gene (SEQ ID NO:2; an exemplary *vanA* gene has SEQ ID NO:1 from *E. faecium* pIP816 gi 43335, also see Figure 1,

> Accession No. X56895 which corresponds to SEQ ID NO:11), or the complement thereof, or a portion thereof; sequences substantially corresponding to nucleotides 870 to 896 of the *vanA* gene (SEQ ID NO:3), the complement thereof, or a portion thereof; sequences substantially corresponding to nucleotides 898 to 917 of the *vanA* gene (SEQ ID NO:4), the complement thereof, or a portion thereof.

The Example discloses the use of primers having SEQ ID Nos. 2 and 4 to amplify *van*A-specific sequences in a sample and a probe having SEQ ID NO:3 to detect *van*A-specific sequences in a sample.

In addition, page 13 discloses that:

> One skilled in the art will understand that probes or primers that substantially correspond to a reference sequence or region can vary from that reference sequence or region and still hybridize to the same target nucleic acid sequence. Probes of the present invention substantially correspond to a nucleic acid sequence or region if the percentage of identical bases or the percentage of perfectly complementary bases between the probe and its target sequence is from 100% to 80% or from 0 base mismatches in a 10 nucleotide target sequence to 2 bases mismatched in a 10 nucleotide target sequence. In one embodiment, the percentage is from 100% to 85%. In another embodiment this percentage is from 90% to 100%; and in yet other embodiments, this percentage is from 95% to 100% (emphasis added).

Page 19 discloses that:

> Preferred methods for detecting the presence of the *vanA* or *vanB* gene, include the step of contacting a test sample with at least two oligonucleotide primers under conditions that preferentially amplify *vanA* and/or *vanB* sequences....While oligonucleotides probes of different lengths and base composition may be used for detecting the *vanA* gene or the *vanB* gene, preferred oligonucleotides have lengths from 15 up to 40 nucleotides and are sufficiently homologous to the target nucleic acid to permit amplification of a *vanA* or *vanB* template and/or hybridization to such a template under high stringency conditions (emphasis added).

Page 19 also discloses that:

> [T]he specific sequences described herein also may be provided in a nucleic acid cloning vector or transcript or other longer nucleic acid and still can be used for amplifying or detecting the *vanA* gene or the *vanB* gene, i.e., the probes may include sequences unrelated to the *vanA* or *vanB* gene, for instance at the 5' end, the 3' end, or both the 5' and 3' ends. Likewise, primers may include sequences unrelated to the *vanA* gene and/or the *vanB* gene, e.g., at the 5' end (emphasis added).

Page 20 discloses that:

> Preferred primers and probes have sequences of up to 40 nucleotides in length and preferably have at least 17 contiguous nucleotides corresponding to sequences in the *vanA* gene or the *vanB* gene, or the complement thereof... Preferably, the probes specifically hybridize to *vanA* or *vanB* DNA only under conditions of high stringency. Under these conditions only highly complementary nucleic acid hybrids will form (i.e., those having at least 14 out of 17 bases in a contiguous series of bases being complementary). Hybrids will not form in the absence of a sufficient degree of complementarity (emphasis added).

Thus, the specification clearly provides support for the recited probes and primers.

Claims 1, 8-9, 15-19, 23, 25, and 44-57 were rejected under 35 U.S.C. § 112, second paragraph. In particular, the Examiner asserts that a) claim 1 is unclear as the broad limitation of probes or primers is that they consist of 15 to 40 nucleotides, yet the narrower range/limitation is drawn to SEQ ID NO:2, 3 and 4 which do not have 40 nucleotides, and the claims and specification fail to disclose what the other nucleotides are; and b) the phrase "effective to form a hybrid" is a relative phrase which renders the claims indefinite. These rejections are respectfully traversed.

The specification discloses that

> [T]he specific sequences described herein also may be provided in a nucleic acid cloning vector or transcript or other longer nucleic acid and still can be used for amplifying or detecting the *vanA* gene or the *vanB* gene, i.e., the probes may include sequences unrelated to the *vanA* or *vanB* gene, for instance at the 5' end, the 3' end, or both the 5' and 3' ends. Likewise, primers may include sequences unrelated to the *vanA* gene and/or the *vanB* gene, e.g., at the 5' end (page 19).

It is also disclosed that

> Preferred primers and probes have sequences of up to 40 nucleotides in length and preferably have at least 17 contiguous nucleotides corresponding to sequences in the *vanA* gene or the *vanB* gene, or the complement thereof... Preferably, the probes specifically hybridize to *vanA* or *vanB* DNA only under conditions of high stringency. Under these conditions only highly complementary nucleic acid hybrids will form (i.e., those having at least 14 out of 17 bases in a contiguous series of bases being complementary). Hybrids will not form in the absence of a sufficient degree of complementarity (page 20).

Therefore, it is Applicant's position that the metes and bounds of the recited primers and probe are clear. That is, the probe is a *vanA*-specific oligonucleotide that forms a double

stranded hybrid with *vanA* nucleic acid in a sample. The probe consists of no more than 40 nucleotides and has a sequence with at least 80% contiguous nucleic acid sequence identity to SEQ ID NO:3 or the complement of SEQ ID NO:3. The probe is one which forms a double stranded hybrid with SEQ ID NO:3 or its complement. Thus, the probe is of a particular length and has sequence homology to SEQ ID NO:3 or its complement.

The two primers are oligonucleotides that amplify *vanA* nucleic acid. The primers consist 15 to 40 nucleotides. One (the first) primer has a sequence with at least 80% contiguous nucleic acid sequence identity to SEQ ID NO:2, and the other (the second) primer has a sequence with at least 80% contiguous nucleic acid sequence identity to SEQ ID NO:4. The first primer forms a double stranded hybrid with the complement of SEQ ID NO:2, and the second primer forms a double stranded hybrid with the complement of SEQ ID NO:4. Hence, the primers are of a particular length and have sequence homology to SEQ ID NO:2 or SEQ ID NO:4.

Moreover, one of skill in the art understands that sequences other than those needed for specificity of a probe or primer may be included with the probe or primer, e.g., a restriction enzyme site may be included in a primer sequence to facilitate cloning of sequences amplified with the primer.

Therefore, the metes and bounds of the recited probe and primers is clear.

It is also Applicant's position that one of skill in the art would understand the metes and bounds of the term "hybrid" as it is conventionally used in the art.

Moreover, even if, assuming for the sake of argument, one of skill in the art would not recognize the metes and bounds of "hybrid", at page 11, it is disclosed that

> a "hybrid" is the complex formed between two single-stranded polynucleotide sequences by Watson-Crick base pairings or non-canonical base pairings between the complementary bases. By "nucleic acid hybrid" or "probe:target duplex" is meant a structure that is a double-stranded, hydrogen-bonded structure, preferably 10 to 100 nucleotides in length, more preferably 14 to 50 nucleotides in length. The structure is sufficiently stable to be detected by means such as chemiluminescent or fluorescent light detection, colorimetry, autoradiography, electrochemical analysis or gel electrophoresis. Such hybrids include RNA:RNA, RNA:DNA, or DNA:DNA duplex molecules.

It is also Applicant's position that the selection of amplification and/or hybridization conditions effective to form a double stranded hybrid between a probe or primer and *van*A sequences is conventional in the art. See, for instance, Petrich et al., *supra,* Patel et al.,

"Multiplex PCR Detection of *vanA*, *vanB*, *vanC*-1, and *vanC-2/3* Genes in Enterococci", J. Clin. Microbiology, 35: 703 (1997); Petrich et al., "Effect of Routine Use of a Multiplex PCR for Detection of *vanA*- and *vanB*- Mediated Enterococcal Resistrance on Accuracy, Costs and Earlier Reporting", Diagnostic Microbiology and Infectious Disease, 41:215 (2001); and Satake et al., "Detection of Vancomycin-Resistant Enterococci in Fecal Samples by PCR", J. Clin. Microbiology, 35:2325 (1997); all of record.

Moreover, one of skill in the art is aware that more than one set of conditions can result in hybrid formation of two nucleic acid sequences.

Thus, the scope of the claims would be clear to a person of skilled in the art, particularly when read in light of the specification.

Accordingly, withdrawal of the § 112 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 onNovember 7, 2008.

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